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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 12/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/718,355	ROULEAU ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/24/2004,*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,8,10,14 and 20-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,8,10,14 and 20-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to amendments, arguments and petition filed 6/24/2004, the reiterated amendments and arguments in the submission dated 9/17/2004, the CRF's submitted 1/3/2005 and 6/5/2005, and the supplemental IDS filed 5/16/2005.

2. Currently, claims 7, 8, 10, 14, 20-30 and newly added claims 31-41 are pending in the instant application, and under consideration. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow, where applicable. This action is FINAL.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The objection made to the specification at section 2, and the rejection under 35 USC 112/first paragraph made at sections 7 and 8 of the previous office action, are moot in view of applicant's explanation in the response dated 6/24/2004 as to the submission to multiple sequence listings as well as the new grounds of objection and rejection submitted below. The sequence listings filed between 11/24/00 and 6/24/04 have been re-reviewed and found not to contain any new matter in light of applicant's explanations. However, it is noted that a 7th

sequence listing was filed 1/3/2005 in response to a "Notice to Comply" mailed 12/8/2004. Additionally, an 8th sequence listing was filed 6/5/2005, however no explanation was provided as to why the 8th sequence listing was filed. Given the number of errors in sequence listings previously submitted, the objection and rejection are newly applied below, with respect to the 7th and 8th sequence listings.

Inventorship

5. In view of the papers filed April 30, 2004, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding inventors Patrick Cossett and David Ragsdale.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Specification

6. The sequence listings filed Jan 2004 and June 2004 are objected to under 35 U.S.C. 132 because they appear to introduce new matter into disclosure. No explanation has been given as to the filing of the sequence listing dated June 2004. Given the number of errors in sequence listings previously submitted, this objection is set forth herein. Applicant is required to either cancel the new matter in the reply to this Office Action, or to provide an explanation as to what

was submitted in the sequence listings filed Jan 2004 and June 2004, and how the changes are supported by the originally filed disclosure dated December November 24, 2000.

7. The specification is also objected to as it contains sequences not followed by an appropriate sequence identifier. An appropriate sequence identifier as set forth in MPEP, chapter 2400, must follow each and every disclosure of a sequence. Appropriate correction is required.

Response to Amendment

8. It is noted that the specification has been amended to provide sequence identifiers for the sequences in pages 52-54 of the specification. However, the disclosure continues to recite sequences without a proper identifier, for example the drawings. Applicant is requested to review the entire disclosure and to provide appropriate sequence identifiers after the disclosure of each sequence. The sequence identifiers for the drawings can be recited in the "Brief Description of the Figures" beginning at page 26 of the specification.

9. The amendment filed 6/24/2004 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the specification was amended to recite "at the amino acid level" at pages 6 and 58. This recitation, however, is not supported by the specification as originally filed. MPEP 2163 [R-1], section B states: "An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only

recognize the existence of the error in the specification, but also recognize the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).". The response asserts that the amendment was made to correct an uncertainty that the disclosed % identity between human and rat sequence was at the nucleic acid level. The response asserts that a blast was conducted for both human neonatal SCN1A (SEQ ID NO: 1) and adult SCN1A (SEQ ID NO: 2) with a known rat sequence and gave 89% identity at the nucleic acid level. The response asserts that based on the fact that the rat and human sequences were known at the time of filing and that the alignments had been performed at the time of the filing, such amendment is not new matter. These arguments have been thoroughly reviewed but were found unpersuasive. As stated in the MPEP, amendments to correct obvious errors do not constitute new matter where one skilled in the art would not only recognize the existence of the error but would also recognize the appropriate correction. In the instant case, no alignment was provided in the specification. Also, given that one of skill in the art would not know if more than one rat sequence would exist, ie: allelic variants, homologs, splice variants, etc, one of skill in the art would not necessarily have recognized that the % identity set forth in the specification was limited to rat and human protein sequences. Therefore, amendment to the specification is considered to add new matter to the disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

Indefinite

10. Claims 7, 8, 10, 14, and 20-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10, for example, is indefinite in the recitation of "providing a screening assay which assess a measurable SCN1A biological activity; contacting said screening assay with a test compound" as it is unclear whether the term assay in claim 10 is referring to a method or a composition. While a composition or a compound can be contacted, a method is a series of steps and the claim does not make clear what is being contacted with the compound. It is unclear if the recitation is intended to indicate whether particular components are being contacted, or whether the term screening assay in this claim is directed to a composition. The specification does not define what the metes and bounds of the term are and therefore the metes and bounds of the claimed recitation are unclear.

Response to Arguments

11. The response asserts that the claim is definite when read in light of the specification. This argument has been thoroughly reviewed but was found unpersuasive. The specification does not make clear what is being contacted in claim 10 when a "screening assay" is provided which assesses measurable SCN1A activity.

12. Claim 39 is indefinite because it is unclear if the blocker and test compound are different or the same. The specification does not make clear whether the products are the same or different. Accordingly, the metes and bounds of the claim are unclear.

Written Description

13. Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER Rejection.

This rejection is reiterated from the previous office action with regard to new submissions to the sequence listing. Sequence listings were filed Jan 2004 and June 2004. No explanation has been given as to the filing of the sequence listing dated June 2004. Given the number of errors in sequence listings previously submitted, this objection is set forth herein. Applicant is required to either cancel the new matter in the reply to this Office Action, or to provide an explanation as to what was submitted in the sequence listings filed Jan 2004 and June 2004, and how the changes are supported by the originally filed disclosure dated December November 24, 2000.

14. Claims 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

The newly added claims 33-38 recite "time course of recovery from inactivation" (claim 33, 34) and assessing flux with "radiolabeled guanidine" (claims 35 and 37). The response provides areas of the specification for support for the newly added claims. The specification was thoroughly reviewed but support for "time course of recovery from inactivation" and "radiolabled guanidine" was not found. The newly added claims are therefore considered to add new matter to the claimed invention.

15. Claims 7, 8, 10, 14, and 20-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite methods requiring "human" SCN1A. Although the specification teaches the sequences of SEQ ID NO: 1 (human neonatal) and SEQ ID NO: 2 (adult human), as well as teaching a few mutations associated with idiopathic generalized epilepsy, the sequences possess very close identity to other mammalian sequences. For example, SEQ ID NO: 1 is 94% and 93% identical to SCN1A nucleic acid sequences for *Canis familiaris* (Accession number XM_535941) and *Bos taurus* (Accession number XM_608042). However neither the specification nor the art describe which differences between the sequences would necessarily be attributed to a "human" vs a "canine" sequence for example, let alone any other mammalian

sequence, or how many of the differences are required to make a sequence "human" vs "canine". While claim 23 recites that the nucleic acid has greater than 95% sequence identity thereto, the specification provides no guidance as to which of the differences found between human and *Canis familiaris*, for example, would indicate that a particular sequence was human vs canine. The response teaches that rat and human SCN1A peptides share 95% identity at the amino acid level. However, the specification provides no indication of what mutations could be tolerated in any mammalian sequences such that they could be distinguished from a "human" sequence, or which mutations would render a mutant mammalian sequence a "human" sequence. Additionally, the recitation of "human" SCN1A specifically encompasses sequences which have not been taught or described by the specification or known in the art at the time the invention was filed. For example, Accession numbers NP_008851 and AAK00217 teach human SCN1A polypeptide sequences which are not disclosed or described by the specification, but are encompassed by the genus recited in the claims.

The claims encompass the use of a broad genus of nucleic acids and proteins which have not been described by the specification. The disclosure of SEQ ID NO: 1 and 2 are representative of the claimed genus of sequences because the specification has not described the genus of mutations or polymorphisms which can occur in SEQ ID NOS: 1-4 such the resulting sequence could be identified as "human". No structure/function correlation has been taught such the skilled artisan would be able to determine what constitutes a "human" sequence from the other closely related mammalian sequences.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NOS: 1-4, or the 3 specific missense mutations set forth in the specification, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Enablement

16. Claims 7, 8, 10, 14, and 20-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for selecting a compound which reduces the activity of the SCN1A sodium ion channel protein selected from the group consisting SEQ ID NO: 3 or SEQ ID NO: 4 comprising:

a) contacting a composition comprising SEQ ID NO: 3 or SEQ ID NO: 4 with a test compound;

b) assaying the activity of the sodium ion channel in the presence of the compound;

c) comparing the activity of the sodium ion channel in the presence of the compound to the activity of the sodium ion channel in the absence of the compound; and

d) selecting a compound that reduces the activity of the sodium ion channel as compared to the activity of the sodium ion channel in the absence of the compound.;

does not reasonably provide enablement for the methods as set forth in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims..

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands,* 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

The claims are broadly drawn to assays for selecting a compound useful for treating any type of epilepsy or neurological disorder associated with an abnormal activity of a voltage gated sodium channel wherein the compound reduced human SCN1A activity of a voltage gated sodium channel by detecting a compound that reduces the activity of the SCN1A sodium channel modulates inactivation of a sodium channel or any activity of a sodium channel (claim 7, 40). The claims are further drawn to methods of selecting a compound for treating wherein the compound reduces SCN1A sodium flux activity (claim 31). The claims are further limited to assaying sodium channel activity, in a method of selecting a compound for treating, by assaying a variety of SCN1A ion channel activities (claims 33-38). The claims are also broadly drawn to selecting a sodium channel blocker useful for treating idiopathic generalized epilepsy or other neurological disorders wherein the blocker affects a human SCN1A sodium channel (claim 39).

The claims are also broadly drawn to identifying a compound which reduces the activity of any SCN1A sodium channel, and more specifically any human SCN1A sodium channel, including from a library of compounds.

The screening methods in the above claims are broadly drawn to administering a compound to any human SCN1A sodium channel, or any fragment thereof, including allelic variants and genomic sequences. Claims 7, 31, 33-40 further require knowledge of a predictive association between compounds which reduce the activity of a sodium channel and their ability to treat epilepsy or any neurological disorder.

The specification has established an association between certain mutations in human SCN1A sodium channel and idiopathic generalized epilepsy (see pages 54-56). For example, the specification teaches that the D188V mutant shifts the state inactivation of membrane potentials

to those that are slightly more positive than observed in wildtype channels. The claims, however, are drawn to compounds that reduce any SCN1A sodium ion channel activity. The recitation of "SCN1A sodium ion channel activity" broadly encompasses any activity, from generally the translation of mRNA to protein, or to binding of the polypeptide to an antibody, as well as more specific activities such as 1) the voltage dependence of activation, a measure of the strength of membrane depolarization necessary to open channels, 2) the voltage dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential, or 3) the time course of inactivation. Furthermore, for example with respect to the recitation of claim 7, the "reduction" encompassed by the compound could be any level of reduction of the sodium channel activity, for which the specification does not teach amino acid residues or specific nucleic acid sequences that are critical for such broadly encompassed "activities".

The specification provides no working examples of any compounds that were screened for reduction of SCN1A ion channel activity, nor any actual screening methods undertaken for selecting any compounds that have any effect on any "SCN1A ion channel activity" or any "reduction" of sodium channel activity, such as sodium flux activity. The specification provides no guidance as to the critical residues that are "functional fragments" of an SCN1A sodium channel, which are encompassed by the claimed recitation. For example, claim 20 now recites that the nucleic acid is any of SEQ ID NO: 189-192, or "allelic variants of such". However, these SEQ ID NOS are drawn to primer sequences which are 15 nucleotides long and would encode a protein with at most 5 amino acid sequences. It is unclear, and the specification provides no guidance as to what SCN1A sodium ion channel activity would be encoded by such

small nucleic acids. Additionally, claim 21 is drawn to any of SEQ ID NOS: 5-32, as well as "allelic variants thereof", however these sequences are fragments of SEQ ID NOS 1 or 2. As the term "SCN1A ion channel activity" is not defined by the specification and does not appear to change the scope of the encompassed activities from the previously recited "biological activity" and therefore broadly encompasses (see pages 19-20) any SCN1A activity from any portion of SEQ ID NO: 1-4. Although the term "functional fragments" has been deleted, the broad range of possible sequences encompassed by the claims (as exemplified by dependent claims 20-21 and 23) also broadly encompasses specific nucleic acid or amino acid "fragments" with any particular activity. The specification, however, has not provided any guidance as to what constitutes a fragment of a human SCN1A nucleic acid sequence that would be required for expression or transcription or translation to protein. The specification has provided no guidance as to critical amino acid residues required for the SCN1A channel activity. Any number and sequence of amino acids could determine specificity of binding to antibodies such that the claim encompass screening for any compound that could effect such a broad scope of activities. Such nucleic acid or amino acid sequences would not necessarily have any therapeutic effect in treating any type of epilepsy or *any* "other neurological disorder". The specification teaches that symptomatic epilepsies have multiple and heterogeneous causes including brain injury, CNS infection, migrational and metabolic disorders. There is no teaching in the specification, however, that a predictable correlation can be made that modulation of SCN1A would be therapeutic in different types of epilepsies with such different causes. Further, the specification provides no predictable correlation that modulation of SCN1A or any fragment or any allelic variant or even any sodium channel would be therapeutic for the broad scope of neurological

disorders encompassed by the claims, such as Alzheimer's disease, Parkinson's disease, schizophrenia, depression, bipolar disorder, etc. Additionally, with regard to "allelic variants" the claims encompass compounds which modulate a large number of sequences that have not been taught or described, as well as unknown nucleic acids and proteins.

The claims have been amended to recite "human SCN1A", however the specification does not provide guidance as to what necessarily distinguishes a "human" sequence from another mammalian sequence. For example, *Canis familiaris* (Genbank Accession number XM_535941) and *Bos taurus* (Genbank Accession number XM_608042) nucleic acid sequences are 94% and 93% identical, respectively, to SEQ ID NO: 1, however neither the specification nor the art teach which differences between the sequences would necessarily be attributed to a "human" vs a "canine" sequence for example, let alone any other mammalian sequence, or how many of the differences are required to make a sequence "human" vs "canine". While claim 23 recites that the nucleic acid has greater than 95% sequence identity thereto, the specification provides no guidance as to which of the differences found between human and *Canis familiaris*, for example, would indicate that a particular sequence was human vs canine. The response teaches that rat and human SCN1A peptides share 95% identity at the amino acid level. However, the specification provides no predictable correlation of what mutations could be tolerated in any mammalian sequences such that they could be distinguished from a "human" sequence, or which mutations would render a mutant mammalian sequence a "human" sequence. Additionally, the recitation of "human" SCN1A specifically encompasses sequences which have not been taught by the specification or known in the art at the time the invention was filed. For example, Genbank Accession numbers NP_008851 and AAK00217 teach human SCN1A polypeptide

sequences which are not disclosed or described by the specification, but are encompassed by the genus recited in the claims.

With regard to compounds and the broad recitation of 'therapeutic" or useful for "treating", the art teaches that such compounds do not necessarily have any structure-function correlation such that a predictable association can be made with a particular class of compounds and therapy or therapeutic effect. For example, Clare (Clare et al; DDT vol. 5, 2000; pages 506-518), teaches that with regard to voltage gated sodium channels as therapeutic targets, drugs differ widely in their therapeutic effect and structure, even those have common binding determinants (see page 509, col. 1). Taylor (Taylor et al, Adv. Pharmacol. Vol. 39, pp 47-98; 1997) teaches that phenytoin, a sodium channel blocker, like anticonvulsants prevent tonic extensor seizures in rodents from maximal electroshock and reduce the severity of seizures, but generally lack activity against clonic seizures and have little or no activity against spontaneous absence seizures in rats (see para bridging pages 74-75). Taylor also teaches, however, that some sodium channel blockers cause seizures (see page 74, para 2).

Therefore, given the lack of guidance from the specification and the unpredictability taught in the art with regard to compounds that modulate sodium channels, undue experimentation would be required of the skilled artisan to practice the invention as broadly as it is claimed. However, the specification provides no working examples of screening assays or compounds that affect SCN1A activity that have a therapeutic effect on any type of epilepsy or any neurological disorder, therefore the skilled artisan would have to screen an extremely large number of different types of compounds to determine if a predictable correlation exists between any compound that "reduces" any SCN1A ion channel activity. The specification does not

provide sufficient guidance as to what constitutes a 'human' sequences vs any other mammalian sequence, or fragments or "allelic variants" of such which possess activity or can be targeted for a reduction in SCN1A ion channel activity such the skilled artisan could predict which sequences could be used in the methods or not. The specification does not provide sufficient guidance as to a therapeutic effect with regard to any type of epilepsy or any neurological disorder and such sequences. The claims encompass an extremely large amount of experimentation requiring extensive trial and error analysis, the results of which are unpredictable, to determine sequences which fall within the scope of the claims or to select compounds with the claimed therapeutic effects. Such experimentation is considered undue.

Response to Arguments

17. The response traverses the rejection. The response asserts that the specification teaches how to make the claimed invention, and teaches numerous cell based and cell free assays that can be used to screen for compounds, teaches how to obtain an SCN1A nucleic acid, ie using expression vectors, as well as teaching the sequences provided in the sequence listing. The response asserts that a number of sodium channel blocker drugs are used to treat epilepsy. The response further asserts that the specification teaches an association between certain mutations in SCN1A and IGE and that such provides a reasonable correlation to the scope of the present claims. The response asserts that because the specification sets forth that SCN1A is implicated in regulation of action potential, SCN1A modulating compounds are useful as therapeutics.

These arguments have been thoroughly reviewed but were not found persuasive. The specification provides general teachings of how to conduct cell based and cell free screening

assays, however such represents teachings of how to find compounds in general, such is not a teaching of how to determine which compounds have a therapeutic effect on epilepsy or any neurological disorder associated with abnormal voltage gated sodium channel activity. Although sodium channel blocker drugs are known, there is no predictable correlation that any compound which reduces SCN1A ion channel activity will be useful as a therapeutic for any type of epilepsy or any neurological disorder associated with an abnormal activity of a voltage gated sodium channel. There are a number of sodium channels, however there is no predictable correlation provided by the specification that a compound which specifically reduces SCN1A activity would target any sodium channel. The teachings of the sequences in the sequence listing and the specific mutations listed in the response does not set forth a predictable correlation as to screening methods for compounds useful in treating epilepsy nor does it provide a predictable correlation as to what constitutes a "human" SCN1A nucleic acid. As set forth above, the sequences of SEQ ID NOS 1 and 2 possess a high level of identity to other mammalian SCN1A sequences, however the specification provides no predictable correlation as to which mutations or variations can be tolerated for the sequences to be considered "human". While specific mutations taught in the specification are found in some patients with epilepsy, and may be associated with epilepsy in some way, the specification has provided no teaching of any compounds which would specifically target such mutations. The specification does not set forth a predictable correlation as to whether compounds could specifically target such mutations, or whether such compounds could then be used as therapeutics. Likewise, while certain specific mutations are taught, the claims encompass a large variable genus of possible human SCN1A sequences. However, the specification provides no indication as to whether such sequences

would have any association with epilepsy (ie: other mutations) or whether targeting such potential mutants would be efficacious in treating epilepsy or any neurological disorder encompassed by the claims. As such, the teachings of the specification do not set forth a reasonable correlation with regard to the broad scope of the claims.

The response asserts that the claims have been amended to recite "human" SCN1A and that the claims no longer recite functional fragments or fragments. This argument has been thoroughly reviewed but is not found persuasive for the reasons set forth in the rejection above. It is noted that the claims continue to encompass fragments given the scope of the dependent claims (ie; claims 20 and 21). With regard to the traversal regarding the term allelic variant, such encompasses a large number of mutant sequences, which would not necessarily be associated with epilepsy. The response asserts that the specification validates that specific mutations in SCN1A affect the function of the sodium channel and refers to examples 3 and 6. This argument has been thoroughly reviewed but was not found persuasive. The mutations in example 3 have not been shown to affect the function of the sodium channel. The specification teaches that the Glu1238Asp mutation is a conservative amino acid change at a residue located in between III-S1 and III-S2 and may influence gating activity. The specification provides no demonstration that such occurs, however, nor does it provide a predictable correlation that any conservative amino acid substitution at that position or generally in SEQ ID NO: 3 or 4 would affect SCN1A activity. The specification also teaches that the Ser1773Tyr mutation is in the middle of IV-S6 TM domain and is interesting because the region it is in was found to play a critical role in fast inactivation in rats. However, the specification does not teach what the critical residues are for this region, or whether the specific mutation at position 1773 altered the

"fast inactivation" activity of SEQ ID NO: 3. The fact that these mutations are found in some patients with epilepsy but not in controls indicates that these mutations may be associated in some way with epilepsy, however such analysis does not indicate which specific role in SCN1A activity, such mutations affect, or if they alter SCN1A activity in any way. Further, the specification provides no predictable correlation between the effect on channel activation that the D188V exhibits and any other mutations in "human" SCN1A. While other mutations could be screened to determine their existence in patients vs controls, and they could also be screened to determine if they have any effect on SCN1A ion channel activity, the ability to screen for additional mutants is not a teaching of what those mutants are or what activity they would alter. There is no predictable correlation between the cited mutants and the extremely large variable genus of mutants encompassed by the claims. As such, the teachings in the specification do not provide a "reasonable correlation" to the entire scope of the claimed invention. Therefore, the response's assertion that the "specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation" is not found persuasive. In the instant case, the specification does not provide a predictable correlation between a compounds' ability to reduce any SCN1A ion channel activity and a therapeutic effect for epilepsy or any neurological disorder associated with an abnormal activity of any voltage gated sodium channel. Additionally, the recitation of specific mutants does not provide a predictable correlation as to the extremely large genus of possible variants and mutants which are encompassed by the claims ('human' SCN1A). Given that the sequences disclosed by the specification possess a large level of identity to other mammalian sequences, the specification does not provide guidance as to what constitutes a

"human" sequence vs another mammalian sequence, other than by SEQ ID NO. It is acknowledged that the specification provides teachings as to how to measure changes in SCN1A channel activity, including the recitation at page 29 of the response, however such teachings are generally related to measuring sodium channel activity. While the specification provides examples of "SCN1A biological activity", these teachings as well as those directed to how to measure changes in SCN1A channel activity do not provide a predictable correlation between a compounds' ability to reduce any SCN1A ion channel activity and a therapeutic effect for epilepsy or any neurological disorder associated with an abnormal activity of any voltage gated sodium channel, nor do they provide a teaching of the extremely large genus of possible variants and mutants encompassed by the claims or how to predictably determine what constitutes a "human" sequence from those of closely related mammalian sequences. Therefore, although such teachings set forth how to generally conduct a screening assay, the argument that the claims are not directed to compounds themselves or to methods of treatment are not persuasive as the claims encompass selecting compounds that are therapeutic as well as requiring that one of skill in the art be able to predictably determine what constitutes "human" SCN1A. The response also asserts that the identification of specific amino acids residues is not required because applicant's were the first to provide the SCN1A gene, it's protein sequences, allelic variants, and validation of SCN1A as a gene involved in a neurological disorder and that such combination of sequence information, validation, and teaching of assays of how to measure SCN1A activity are useful to identify compounds that modulate SCN1A activity. This argument has been thoroughly reviewed but was found unpersuasive. The claims are broadly drawn to providing *any* "human" SCN1A, however, as set forth above, the specification has provided no teaching, other than by

SEQ ID NO:, and the example of a few amino acid substitution, what constitutes a "human" sequence, or how one of skill in the art would be able to predictable determine or distinguish a 'human' sequence from that of other close structurally related mammalian SCN1A sequences. Additionally, the claims broadly encompass any variant of 'human' SCN1A, however the specification has provided no predictable correlation that any variant would be involved in epilepsy or neurological disorder, such that there is no predictable correlation that any compound which would modulate such a broad variable genus of possible sequences would be useful to treat epilepsy or any neurological disorder associated with an abnormal activity of a voltage gated sodium channel. The specific mutations provided by the specification do not establish a predictable correlation as to other possible disease "associated" mutations, nor do they establish a universal correlation between the presence of a mutation and an association with epilepsy or any neurological disorder associated with an abnormal activity of a voltage gated sodium channel. For these reasons, and the reasons made of record above, and in the previous office action, the rejection is maintained and newly applied to the amended and newly added claims.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 8, 10, 14, 20, 21, 23-30, 32, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Malo (Malo et al; Cytogenet. Cell Genet. Vol. 67, pages 178-186, 1994) and Denyer (Denyer et al; Drug Discovery Today, vol. 3, pages 323-332, 1998).

The claims have been broadly interpreted to encompass fragments of SCN1A.

With regard to claims 8, 10, 14, 20, 21, 23, 28-30 and 32, Malo teaches the identification of four human sodium channel gene sequences, as well as a 1.6 kb fragment which has 95% and 94% nucleotide and amino acid level homology with rat SCN1A (see abstract, fig 2, fig 3). Malo teaches that this sequence was localized to chromosome 2q24 and teaches that this sequence is from human brain sodium channel gene, SCN1A, more specifically exon IIIS5 (figure 3). Malo teaches cloning such sequence into vectors as well as FISH analysis (see page 179, cols 1-2). Malo teaches that such localization for SCN1A as well as SCN2A sets the stage for their evaluation in families with neuropsychiatric dysfunction and other genetic diseases. Malo does not teach screening for compounds that reduces the activity of a human SCN1A, however Denyer teaches that voltage gated ion channels are emerging as a target class of increasing importance to the pharmaceutical industry (see abstract). Denyer teaches voltage gated ion channel families such as sodium channel alpha subunit from brain (se page 324). Denyer teaches that designing high throughput screens for voltage gated ion channels requires a different

approach than for other receptors or ligand gated ion channels because of the nature of the activation process and teaches that sites are identified experimentally to be important in conformational transitions of channels and that such sites may be exploited in drug discovery programs. With regard to claims 8, 10, 24-30, 32, and 41, Denyer specifically teaches high throughput ion channel assays include functional and radioligand-binding approaches applies to cells, vesicles or membranes, expression native or cloned channels, or to whole cell assays (see page 325, col. 1, 1st and 2nd full para). Denyer teaches that whole cell assays may use electrophysiological techniques such as patch clamping, and that kinetics of ion flux through open channels can be measured using fluorescence or cell viability techniques. Denyer teaches that typically, screening programmes are designed to assay 50,000 to 200,000 samples or to employ compound sets, allowing the ability to perform highly automated, high density assays which increases the chances of discovering and exploiting completely novel chemical leads. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to provide a screening assay for compounds that modulate SCN1A ion channel activity by assaying a compound, from a library of test compounds, for compounds that modulate the activity of SCN1A because Denyer teaches that voltage gated ion channels are emerging as a target class of increasing importance to the pharmaceutical industry and that typically, screening programmes are designed to assay 50,000 to 200,000 samples or to employ compound sets, allowing the ability to perform highly automated, high density assays which increases the chances of discovering and exploiting completely novel chemical leads. Although Denyer does not teach a specific sequence of SCN1A, Malo teaches a human SCN1A sequence and Denyer teaches that sites are identified experimentally to be important in conformational

transitions of channels and that such sites may be exploited in drug discovery programs. The ordinary artisan would have been motivated to use the sequences taught by Malo in a screening assay for compounds that modulate SCN1A activity because Denyer teaches performing such high throughput assays increases the chances of discovering and exploiting completely novel chemical leads.

Conclusion

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. No claims are in condition for allowance.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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11/28/05